REMARKS

Claims 8-53 are pending in the present application.

The rejection of Claims 8, 9, 12, 13, 16-19, 22, 23, and 26-32 under 35 U.S.C. §102(b) over Barry et al (US 5,055,306) is respectfully traversed.

The present invention is drawn to "a pharmaceutical composition comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides:

- a maximum plasma concentration of levodopa at about 0.3 hours (T_{max}) after said administering" (claim 8);
- a mean maximum plasma concentration of levodopa (C_{max}/dose) of about 9.6 ng/mL/[mg LDME] after said administering" (claim 12);
- an area under the curve of levodopa in plasma from 0 to 1 hour (AUC_{1h}/dose) of about 5.3 ng·hr/mL/[mg LDME] after said administering" (claim 17);
- a ratio of about 2.7 of mean plasma concentration of levodopa at 15 minutes after said administering compared to 60 minutes after said administering"(claim 22);
- a mean plasma concentration (C_p) of levodopa of about 8.8 ng/mL/[mg LDME] 15 minutes after said administering" (claim 26).

and wherein:

- said acid-base couple is sodium glycine carbonate -fumaric acid (claims 9, 13, 19, 23, and 32);
- said composition further comprises carbidopa monohydrate (claims 10, 14, 20, 24, and 33); and

- the weight ratio of levodopa methyl ester to carbidopa monohydrate to sodium glycine carbonate to fumaric acid is about 1.0:0.09:1.7:1.1, respectively (claims 11, 15, 21, 25, and 34).

In particular the composition of the present invention:

- because of its light effervescence and rapid disintegration is a *fast dissolving* formulation
- after single oral dose administration show a more *rapid absorption* and an active ingredient higher exposure during the *first hours after administration* in comparison to the standard commercial formulation (see paragraph [0116]).

In fact all the pharmacokinetics parameters detailed in the independent claims relate to the fast oral absorption profile of levodopa and carbidopa released from effervescent tablets according to the present invention. Applicants respectfully submit that Barry et al fails to disclose, explicitly or implicitly, or suggest all the limitations of the claims and, thus, fails to anticipate the claimed invention. For the Examiner's reference, Applicants submit the following detailed summary of the deficiencies in Barry et al.

In contrast to the present invention, Barry et al discloses "a granular sustained-release formulation of a pharmacologically active substance presented in the form of a tablet, said tablet comprising sufficient granules to provide a predetermined dose or number of doses of the pharmacologically active substance and effervescent or water-dispersible ingredients, each of *said granules* preferably having a diameter of between 0.5 and 2.5 mm and comprising:

a) *a core* comprising one or more pharmacologically active substances and preferably one or more excipients; and

b) *a coating covering substantially the whole surface of the core* and comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative, the weight of the coating being from 2 to 25% of the weight of the core." (see column 3 lines 37 to 53, emphasis added)

Moreover Barry et al states: "the formulations of this invention are thus presented in the form of tablets which disintegrate into *sustained-release -granules* upon coming into contact with an aqueous liquid." (see column 4 lines 6 to 9, emphasis added)

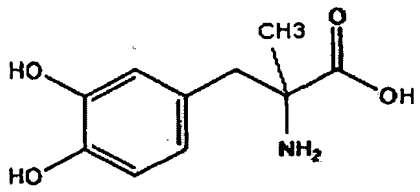
Therefore, even if Barry et al describes effervescent tablets comprising, in the effervescent couple, maleic acid, fumaric acid or its monosodium salt and glycine sodium carbonate, these formulations are applied to *sustained-release granules* comprising a core, including the active ingredient, coated by "a water insoluble but water swellable acrylic polymer and a water soluble hydroxylated cellulose derivative" (see column 6, line 34 to 35), to provide a sustained release over a period of 12 to 24 hours (see column 5, line 64 to column 6, line 9). In contrast, the composition of the present invention is a typified by the fast dissolution and rapid absorption of the active ingredient constituted by the combination levodopa methyl ester + carbidopa (see Example 19).

Moreover, Barry et al suffers an even more fatal flaw with respect to the claimed invention. At no point do Barry et al disclose or suggest the required claim element of levodopa methyl ester. Barry et al only generally discloses among the pharmacologically active substances appearing in column 7, lines 3-46 that the active ingredient in their sustained-release formulations include:

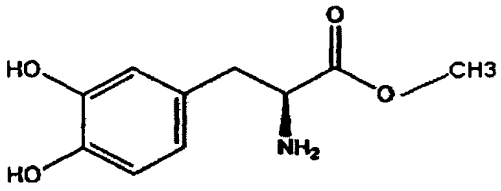
- anti-hypertensives e.g. methyldopa, levodopa and prazosin (see column 7, lines 12-13); and
- antiparkinsonism drugs e.g. benzhexol, levodopa) (see column 7, lines 28-29).

However, at no point is levodopa methyl ester, or even carbidopa disclosed.

Based on the Office Action on page 3, it appears that the Examiner is alleging that the foregoing recitation from column 7 contains a disclosure of levodopa methyl ester. Applicants respectfully disagree. It appears that the Examiner's allegation relates to the disclosure of methyldopa, which is an antihypertensive drug, not an antiparkinsonism drug. However, methyldopa (I) is structurally distinct from levodopa methyl ester (II) as illustrated below:



(I)



(II)

The Examiner is reminded that in order for a reference to anticipate an invention, the reference "must teach every element of the claim" (MPEP §2131). In view of the foregoing, in particular the failure of Barry et al to disclose or suggest the required active ingredient - levodopa methyl ester, Applicants submit that Barry et al fail to anticipate the claimed invention.

Accordingly, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 8-34 under 35 U.S.C. §102(b) over Chiesi (US 4,826,875) in view of Barry et al (US 5,055,306) is respectfully traversed.

With respect to the combined disclosures of Chiesi and Barry et al, Applicants respectfully submit that the skilled artisan would have no motiviation to combine these disclosures and that the present invention would not be obvious in view of this combination.

As stated above, Barry et al is directed to "granular sustained-release formulation... comprising:

a) *a core* comprising one or more pharmacologically active substances and preferably one or more excipients; and

b) *a coating covering substantially the whole surface of the core*" (see column 3 lines 37 to 49, emphasis added)

which provides a sustained release over a period of 12 to 24 hours (see column 5, line 64 to column 6, line 9) and enables large dosages in sustained release form to be more easily swallowed by the patients than previously known formulations (see column 4, line 67 to column 5, line 7).

In contrast, in Chiesi it has been found that levodopa methyl ester can be used as active principle of pharmaceutical compositions with surprising therapeutic effects in all kinds of parkinsonism and in the neurologic syndromes related to it. In particular, Chiesi describes pharmaceutical compositions for oral or sublingual administration in solid (i.e. tablets) or liquid form. The compositions described, which may contain levodopa methyl ester in combination with benserazide, carbidopa or deprenyl, do not contain an effervescent couple.

Even if Barry et al were combined with Chiesi, it would not be possible to reach the same results of the present invention, since the coating on the core disclosed by Barry et al

containing the active ingredient would lead to a controlled/retarded release of the active ingredient.

Further, it would not be possible, among components of the effervescent couple cited in Barry et al, to select the components described in the present invention (e.g., glycine, sodium carbonate and fumaric acid) in order to obtain effervescent tablets having fast dissolution and rapid absorption in the first hour after administration. This is shown by the following pharmacokinetics parameters:

- T_{max} (i.e., time to maximum concentration)
- C_{max}/dose (i.e., mean maximum plasma concentration /dose [mg LDME])
- AUC_{1h}/dose (i.e., area under the curve of levodopa in plasma from 0 to 1 hour/dose [mg LDME])
- ratio of mean plasma concentration of levodopa at 15 minutes after administration compared to 60 minutes after said administration,
- mean plasma concentration of levodopa (C_p) 15 minutes after said administration.

Further, the values of these parameters, claimed for the formulation of the present invention (See Example 19, Table 8 and claims 8, 12, 17, 22, 26) as compared with the calculated values based on the data reported in Example 8, Table 1 of Chiesi are as follows:

	Claimed invention	Chiesi (calculated)
T_{max} (claim 8)	About 0.3 h	0.75h
C_{max}/dose (claim 12)	About 9.6 ng/mL/[mg LDME]	6.0 ng/mL/[mg LDME]
AUC_{1h}/dose (claim 17)	about 5.3 ng·hr/mL/[mg LDME]	4.3 ng·hr/mL/[mg LDME]
ratio of mean plasma concentration of levodopa at 15 minutes after administration compared to 60 minutes after said administration (claim 22)	About 2.7	0.83
mean plasma concentration of levodopa (C_p) 15 minutes after said administration (claim 26)	About 8.8 ng/mL/[mg LDME]	3.5 ng/mL /[mg LDME]

Therefore, it can be observed that the formulations of effervescent tablets for the present invention showed a more rapid absorption and an active ingredient higher exposure during the first hours after administration with respect to the formulation of the Chiesi. The skilled artisan would not be motivated to modify Chiesi or obtain these results when combining this disclosure with Barry et al. This is particularly true when considering that the formulation disclosed by Barry et al is a suspended-release formulation.

In view of the foregoing, Applicants submit that the presently claimed invention is not obvious in view of the combined disclosures of Chiesi and Barry et al. As such, withdrawal of this ground of rejection is requested.

Applicants request that the obviousness-type double patenting rejection of Claims 8, 10, and 11 over Claim 1 of U.S. 6,284,272 be held in abeyance until such a time as allowable subject matter is identified. At that time, if necessary, a Terminal Disclaimer will be filed. Until this occasion, Applicants make no statement with respect to the propriety of the Examiner's rejection.

Finally, with respect to the withdrawn method claims, the Examiner is reminded that MPEP §821.04 states:

> ...if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.

Applicants note that should the examined product claims (i.e., Claims 8-34) be found allowable, withdrawn process claims (minimally Claims 35-48) should be rejoined and examined as these claims contain all the limitations of the examined product claims. An action to this effect is requested.

Applicants submit that the present application is now in condition for allowance.

Early notification of such action is earnestly solicited.

Respectfully submitted,

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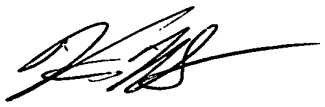
MAIER & NEUSTADT, P.C.



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